Armed Forces College of Medicine

AFCM

Sphingolipidoses 1

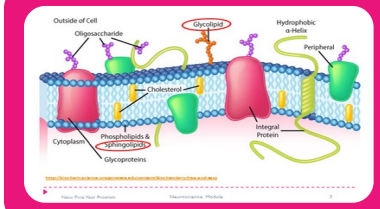
Dr. Naglaa Fathy, MD

INTENDED LEARNING OBJECTIVES (ILOs)

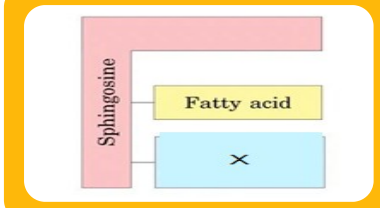
- **By the end of this lecture, You will be able to:**

1. **Understand the meaning of sphingolipidoses.**
2. **Illustrate the difference between Phospholipids & Sphingolipids.**
3. **Discuss the synthesis and degradation of different sphingolipids.**

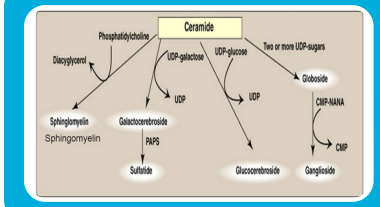
Contents:



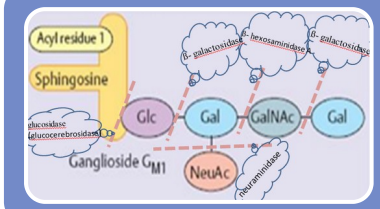
What is meant by sphingolipidoses?



What are sphingolipids?



Synthesis of sphingolipids

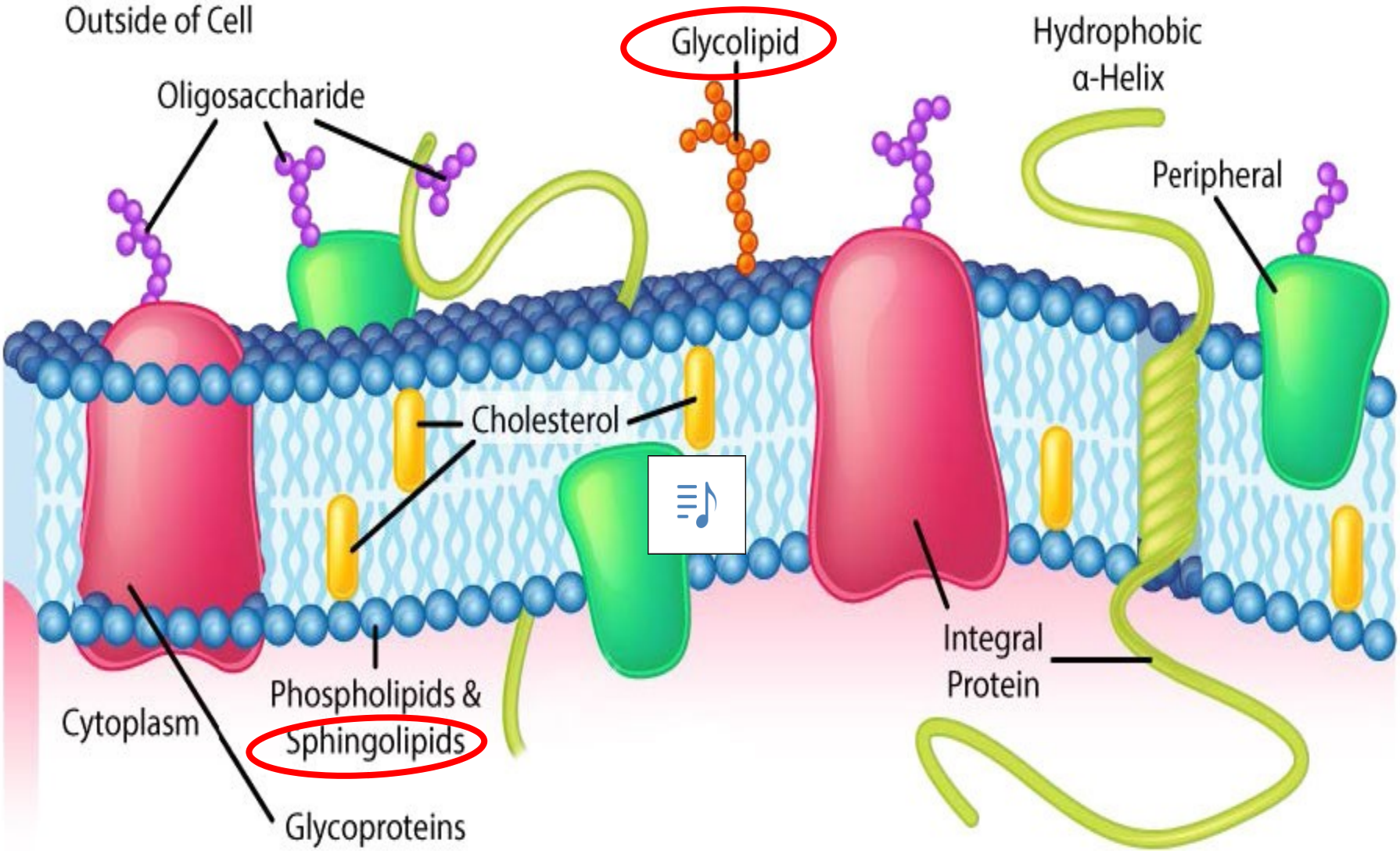


Overview on sphingolipids catabolism

https://www.researchgate.net/publication/
2679543[illegible]ype_I_Gaucher_disease_GDI_in_three_siblings_enzym
e_replace[illegible]ent_treatment_ERT_required

https://www.dailylocal.com/news/
national/irish-ancestry-focus-of-tay-sachs-
families/article_e01ba0d2-3f50-5a60-
a6[illegible]-bbe5a3e63ba6.html

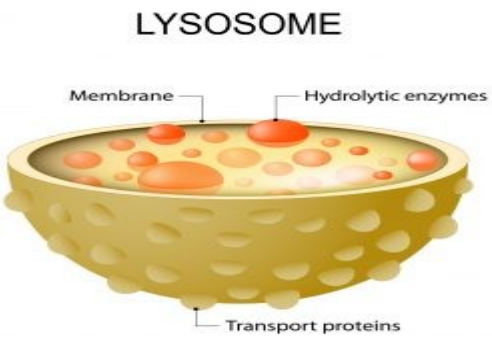
vital signs
https://edition.cnn.com/2014/11/21/health/hem[illegible]els-genetic-
disorder-niemann-pick/index.html



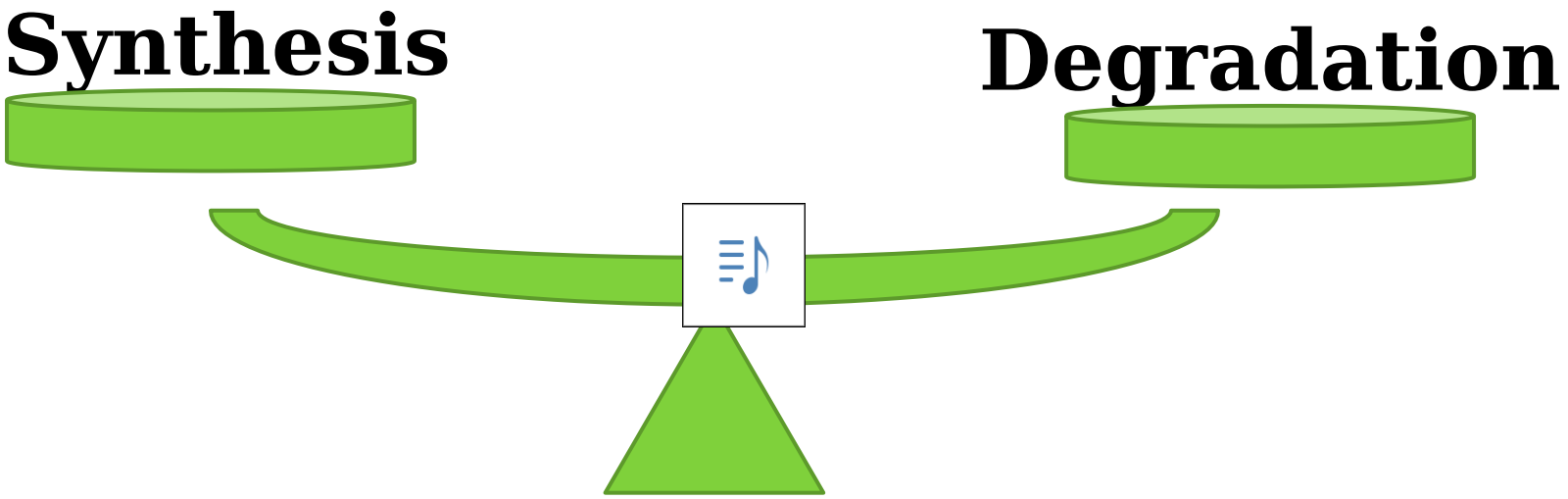
http://biochem.science.oregonstate.edu/content/biochemistry-free-and-easy

Sphingolipids; Catabolism:

- **Sphingolipids are released when a membrane is degraded**
- **Internalized into endosomes**
- **Digested after fusion with lysosomes which contain acid hydrolases (active at a pH of 5).**

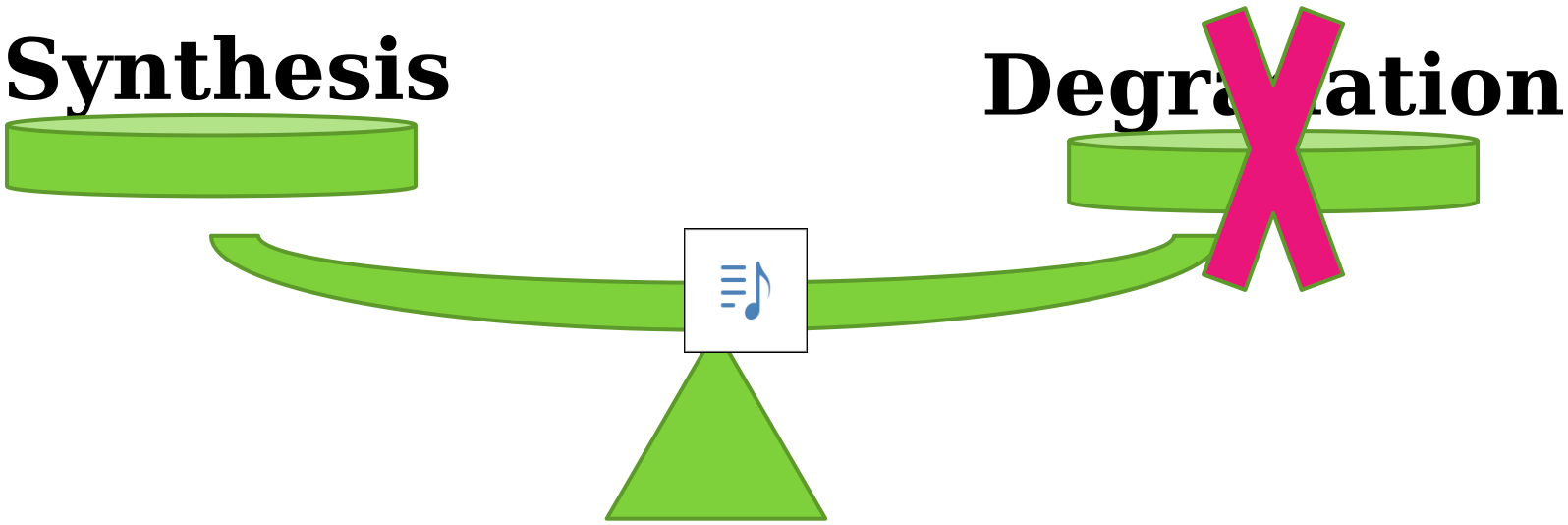


Sphingolipids; Catabolism:



- **Normally, synthesis and degradation of glycosphingolipids are balanced, so that the amount of these compounds present in membranes is constant.**

Sphingolipids; Catabolism:



Sphingolipidoses (Lipid Storage Diseases)

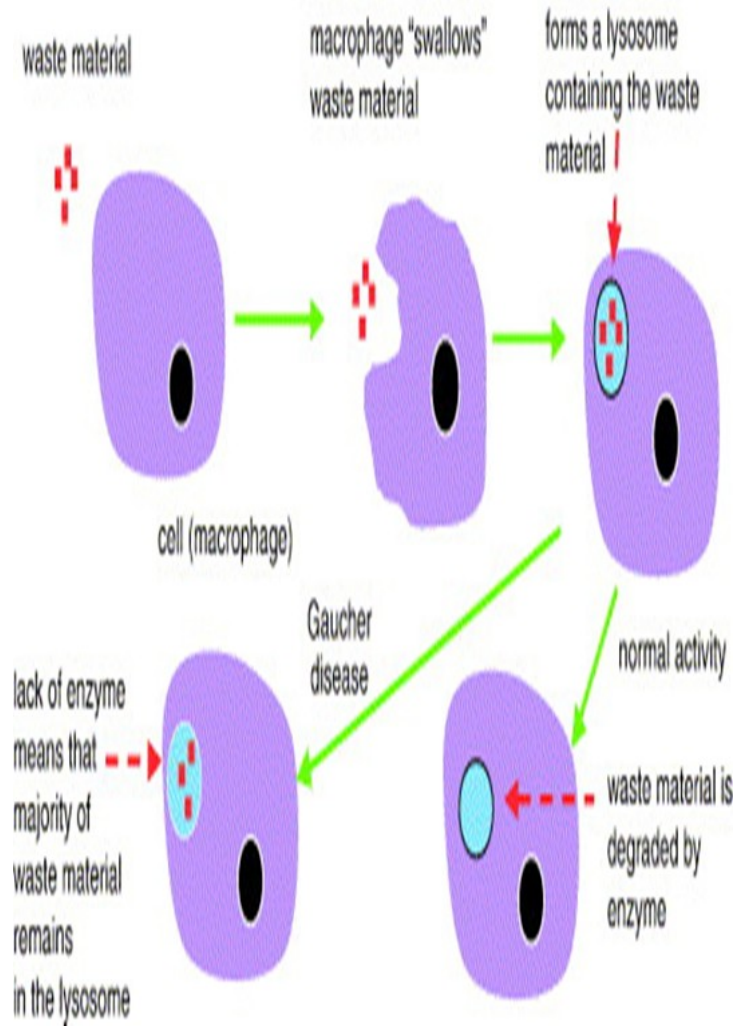
They are part of a larger group of lysosomal disorders

Sphingolipidoses

- **Accumulation of any type of sphingolipids**

Seen dramatically in nerve tissue

Neurologic deterioration and early death

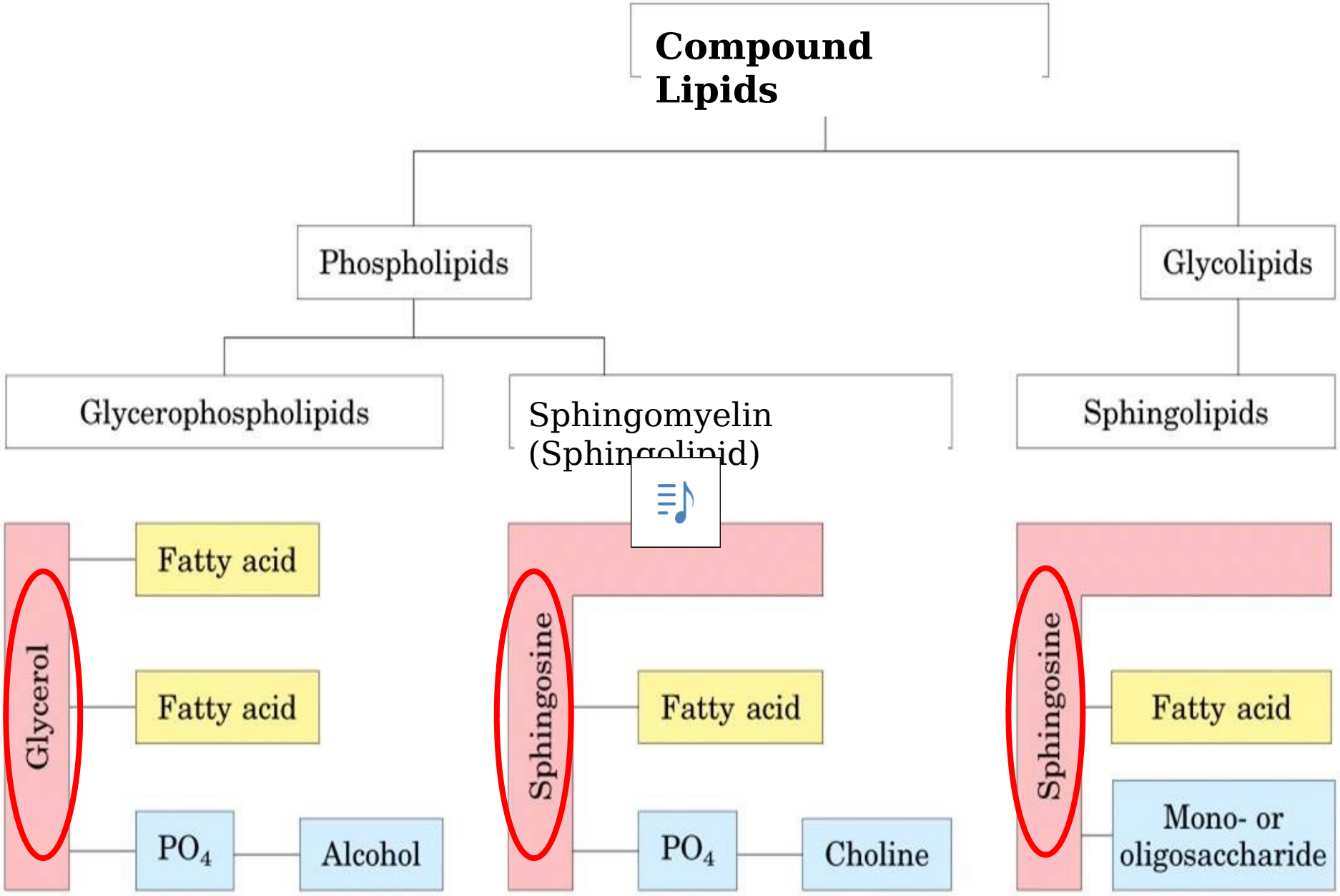

waste material
macrophage "swallows" waste material
forms a lysosome containing the waste material
cell (macrophage)
Gaucher disease
normal activity
lack of enzyme means that majority of waste material remains in the lysosome
waste material is degraded by enzyme

Epidemiology and natural history of Gaucher's disease. Mehta A et al. Eur J Intern Med. (2006)

A patient was diagnosed with one of the types of sphingolipidoses. The deficient enzyme normally carries out which of the following functions?

A. Degradation of glycogen in muscles
B. Degradation of glycolipids in the brain
C. Degradation of mucopolysaccha
bone marrow.
D. Synthesis of glycoproteins in the
E. Synthesis of peptides in the sple

What Are Sphingolipids?

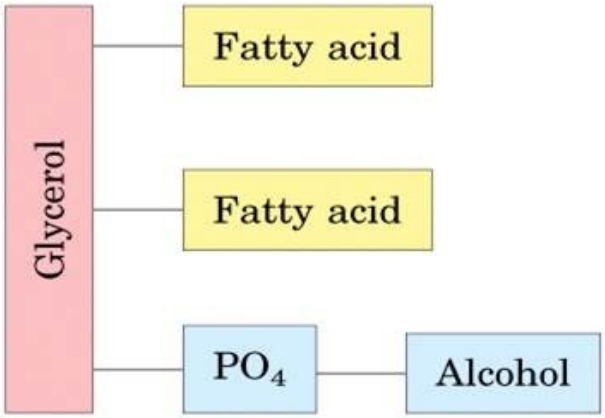


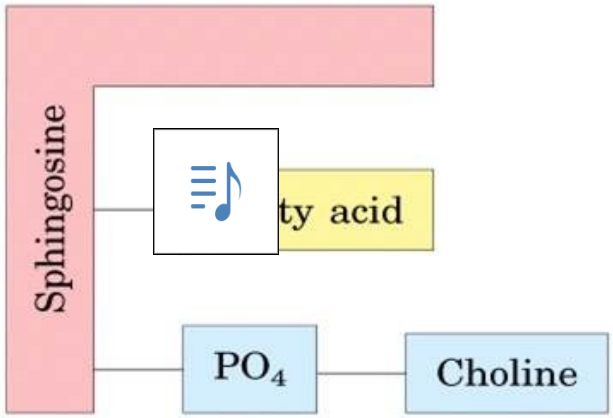
Edited from:: https://phys.libretexts.org/Courses/University_of_California_Davis/UCD%3A_Biophysics_241_-_Membrane_Biology/1%3A_Lipids/Lipid_Headgroup_Types

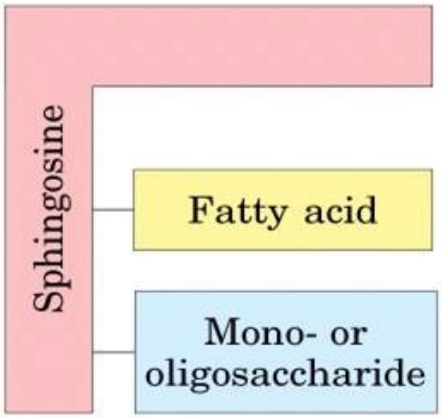
Glycerophospholipids

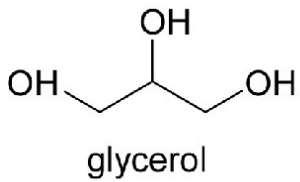
Sphingomyelin

Glycolipids

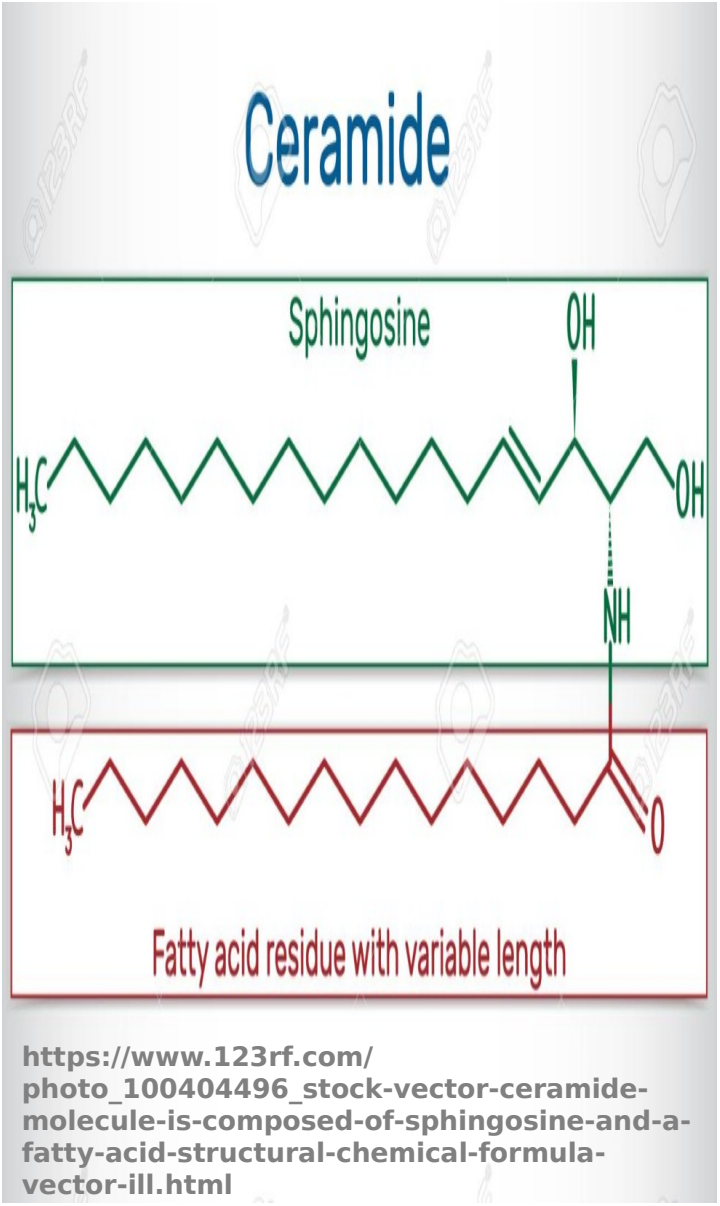






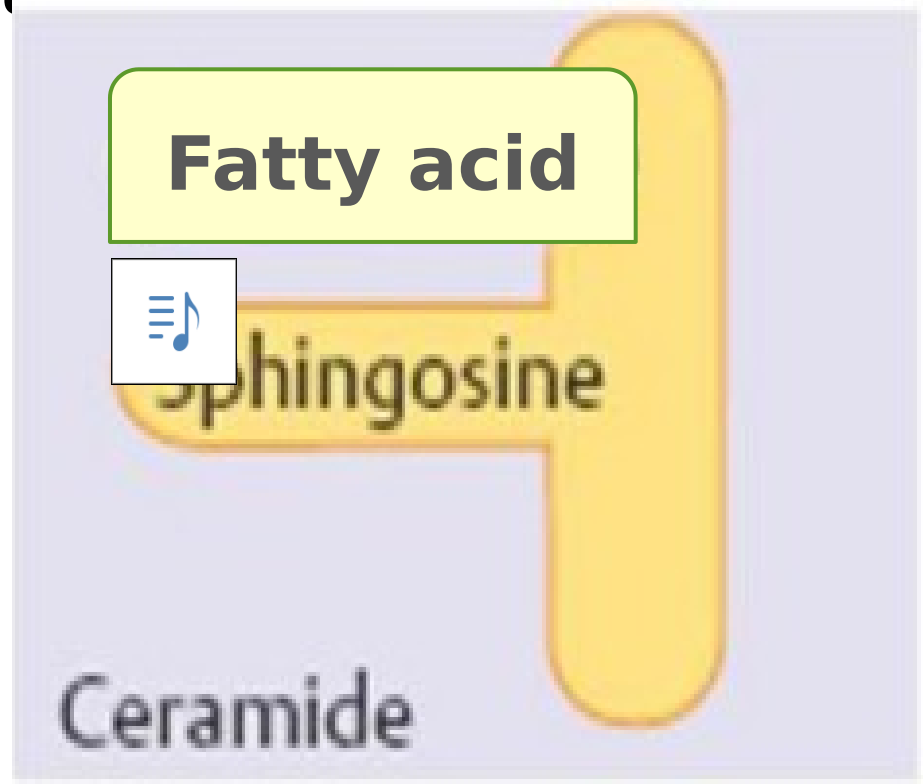


Edited from:: https://phys.libretexts.org/Courses/University_of_California_Davis/UCD%3A_Biophysics_241_-_Membrane_Biology/1%3A_Lipids/Lipid_Headgroup_Types



https://www.123rf.com/photo_100404496_stock-vector-ceramide-molecule-is-composed-of-sphingosine-and-a-fatty-acid-structural-chemical-formula-vector-ill.html

Ceramide = Sphingosine + fatty a



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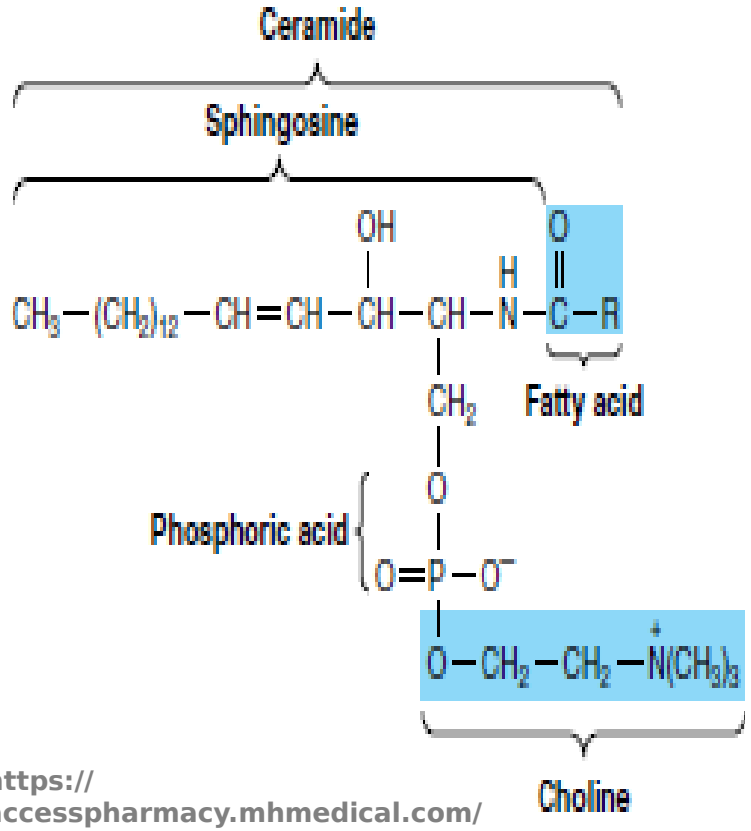
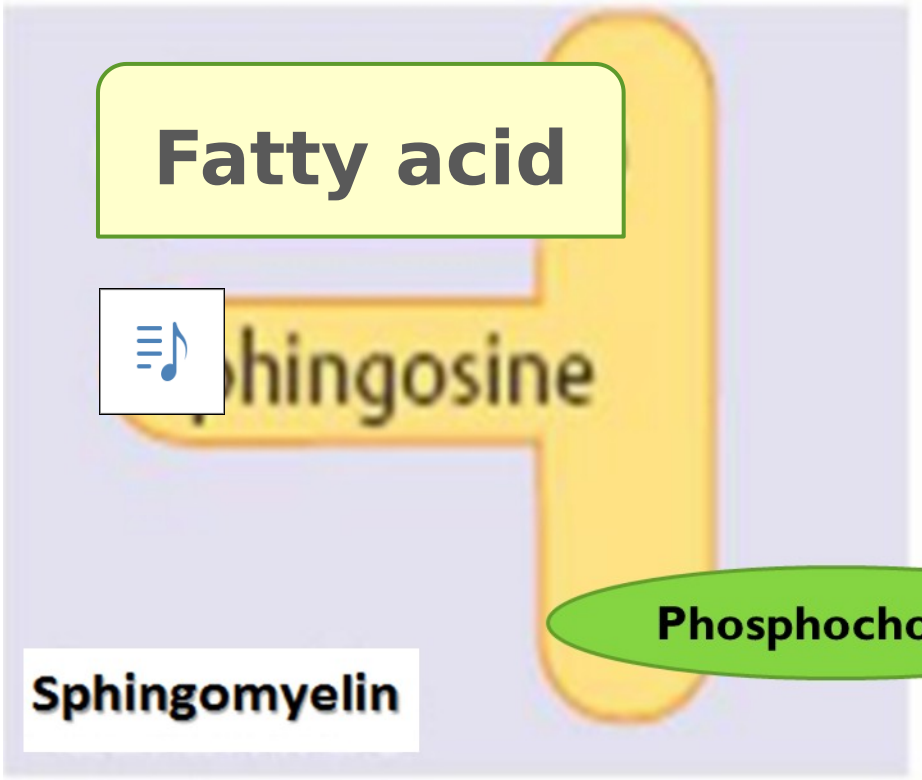
Sphingomyelin is a major structural lipid in the membranes of nerve tissue .



https://accesspharmacy.mhmedical.com/content.aspx?bookid=1696&sectionid=111399035



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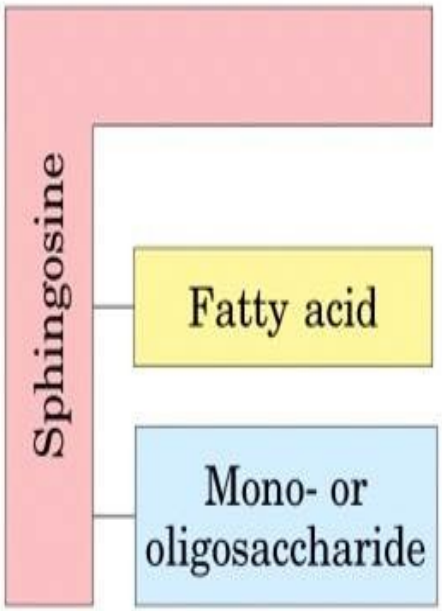
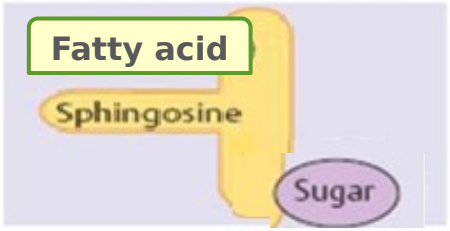
Sphingomyelin = Ceramide + Phosphocholine

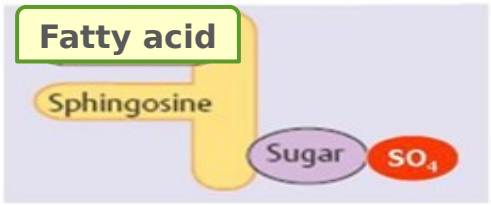
Glycolipids



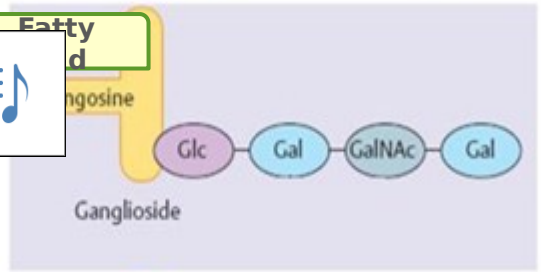
Cerebrosides



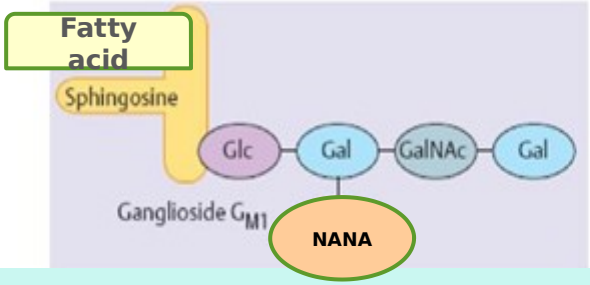
Sulfatides



Globosides



Gangliosides



Glycolipids = Ceramide + Carbohydrates

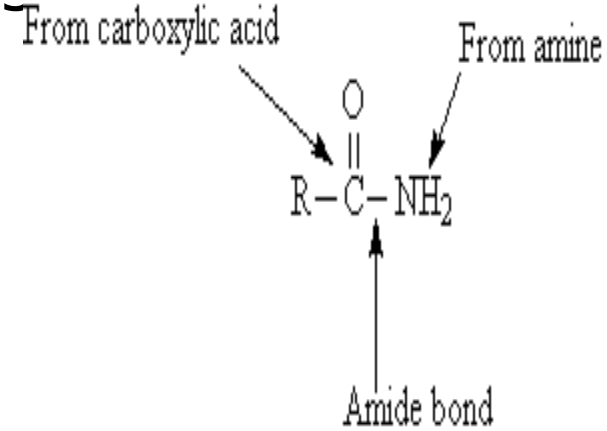
Edited from: https://slideplayer.com/slide/12976068/

A patient was diagnosed with one of the types of sphingolipidoses. All sphingolipids have in common which one of the following?

A. A glycerol backbone
B. Ceramide
C. Phosphorylcholine
D. *N*-acetylneuraminic acid (NANA)
E. A steroid ring structure to which sphingosine is attached

Sphingolipids; Synthesis:

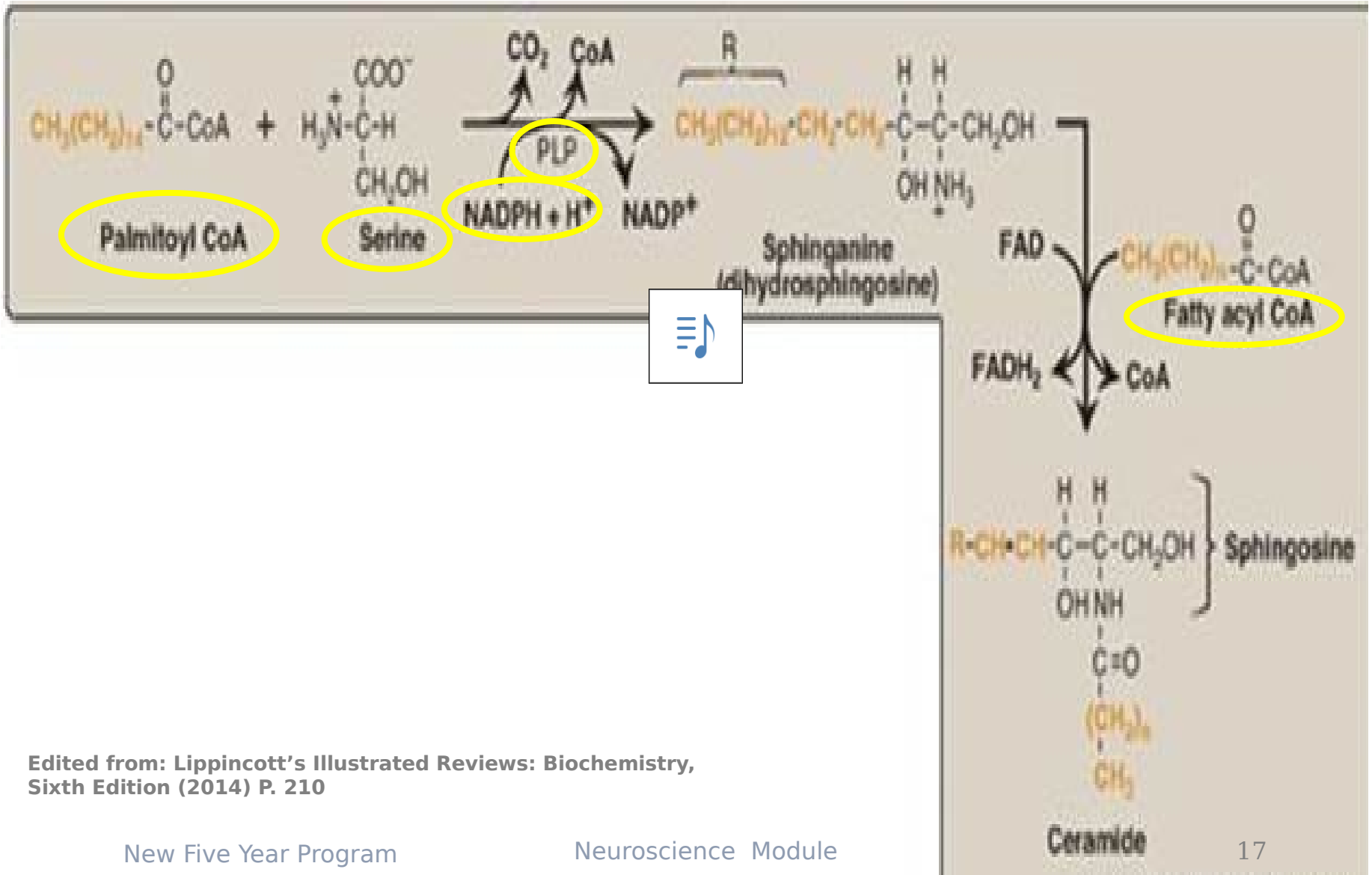
1. **Synthesis of ceramide** (sphingosine connected by an amide linkage to acyl group).



https://chemistry.stackexchange.com/questions/49219/is-the-chemical-structure-of-an-amide-bond-conh-or-conh2?rq=1

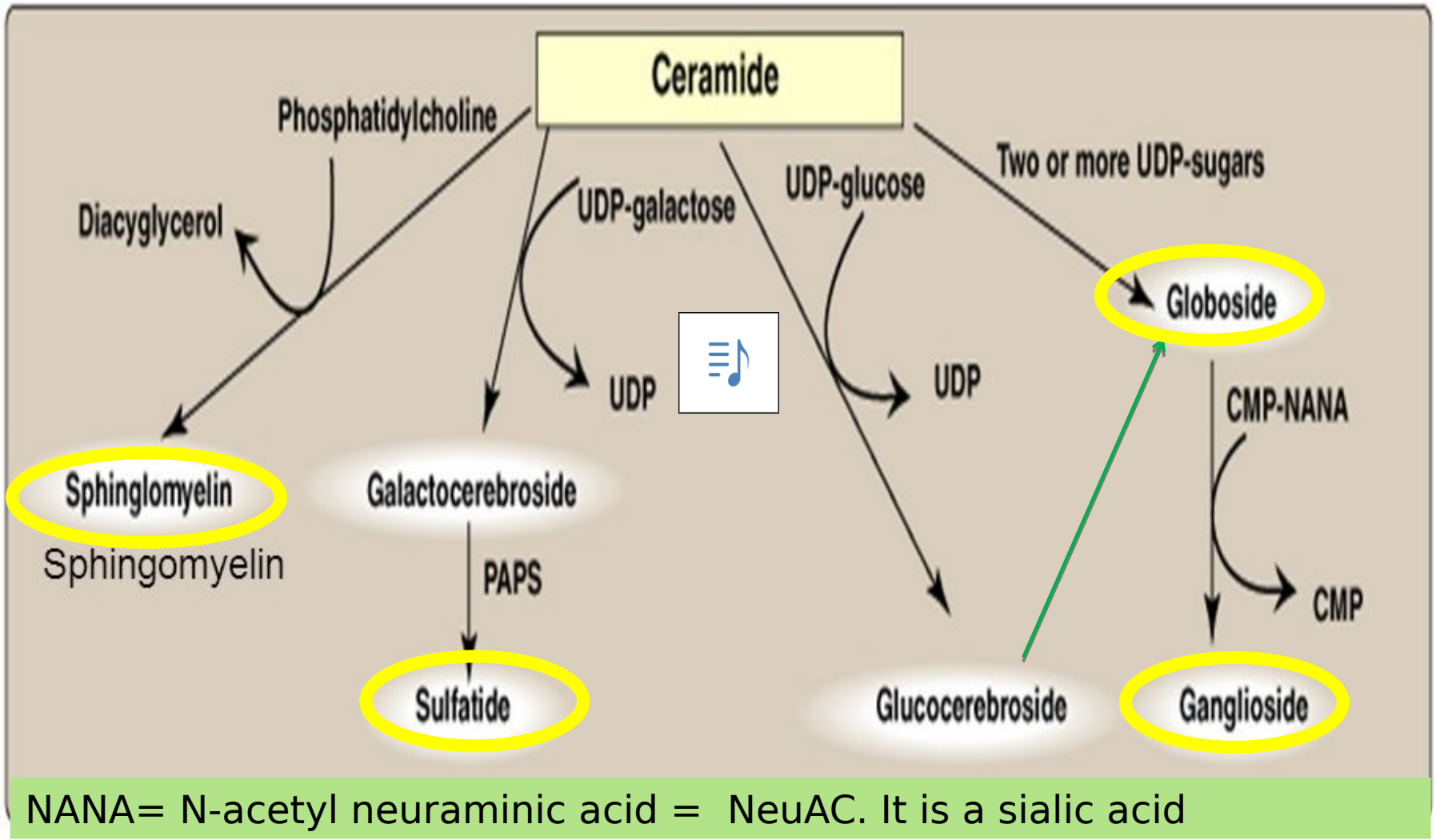
2. **Synthesis of the Different Sphingolipids**

Synthesis of Ceramide:



Edited from: Lippincott's Illustrated Reviews: Biochemistry, Sixth Edition (2014) P. 210

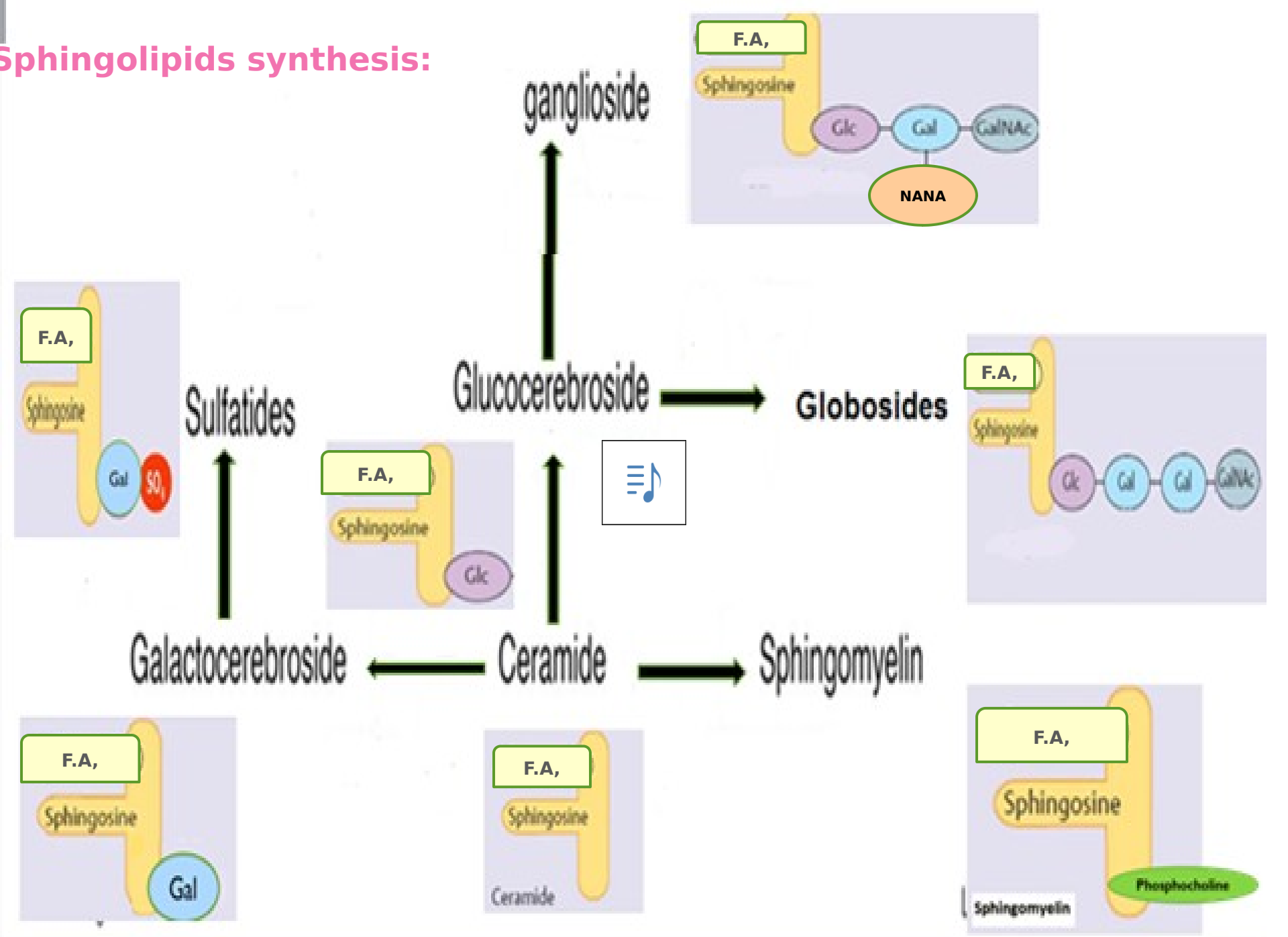
Synthesis of the Different Sphingolipids



NANA= N-acetyl neuraminic acid = NeuAC. It is a sialic acid

Lippincott's Illustrated Reviews: Biochemistry, Sixth Edition (2014) P. 214 (Edited with the green arrow)

Sphingolipids synthesis:

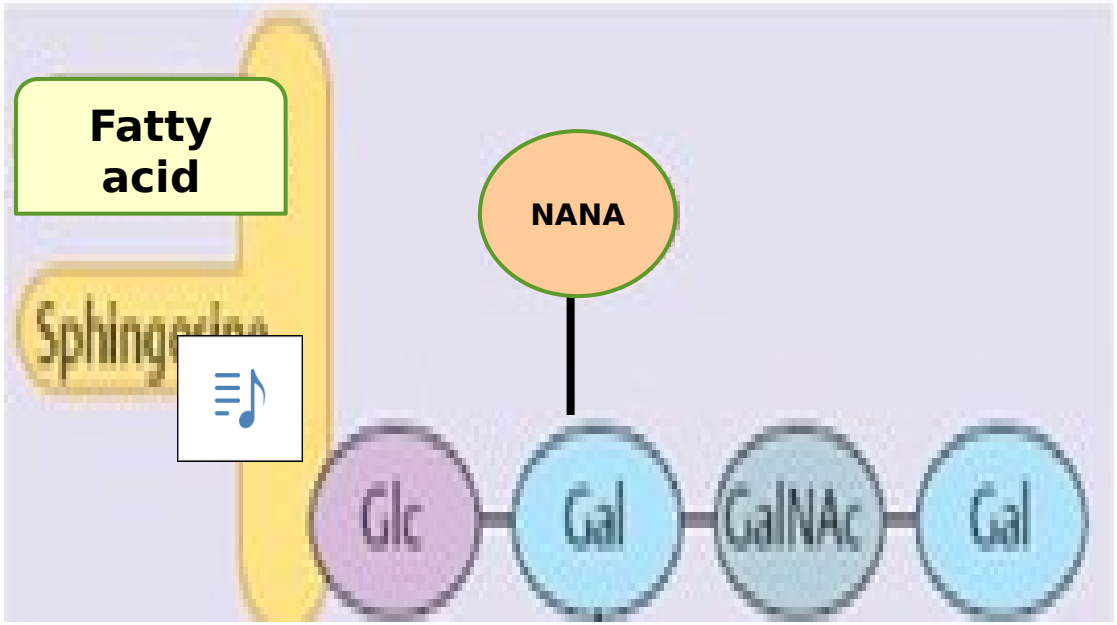


For synthesis of a globoside, the following may be involved:

A. Sulfate
B. UDP- Glucose
C. Phosphorylcholine
D. *N*-acetylneuraminic acid (NANA)
E. A steroid ring

Gangliosides

Gangliosides



G= Ganglioside
M= Mono (one NANA)

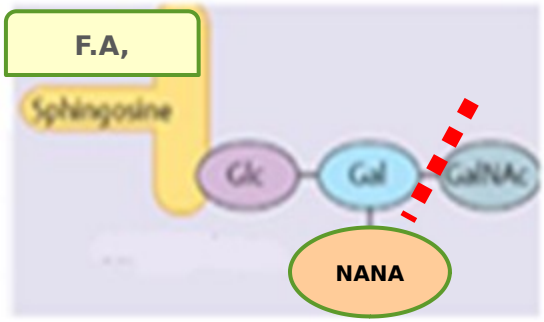
GM3

GM2

GM1

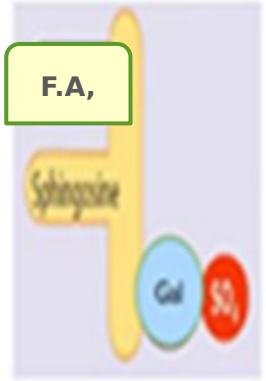
Edited from: https://slideplayer.com/slide/12976068/

Sphingolipid Catabolism:



GM_2 ganglioside

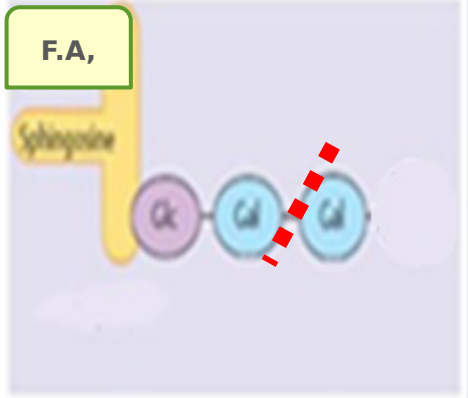
hexosaminidase

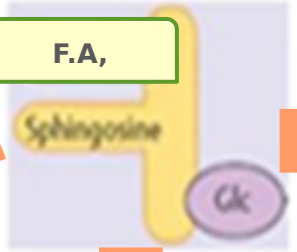


Sulfatides

α- galactosidase

Glucocerebroside ← Globosides





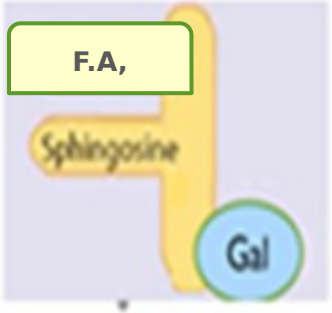
Arylsulfatase

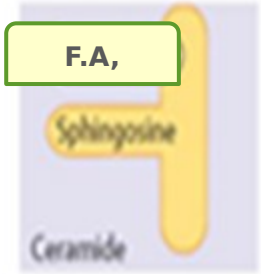
Glucocerebrosidase

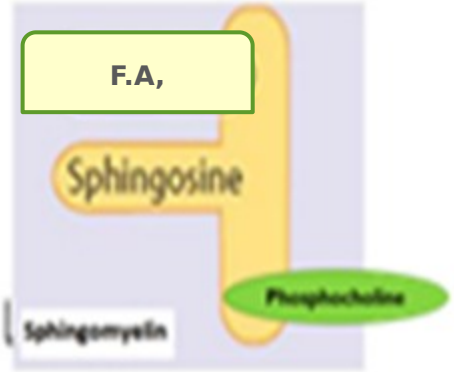
Galactocerebroside → Ceramide ← Sphingomyelin

Galactocerebrosidase

Sphingomyelinase







Key Points

- Sphingolipidoses are congenital diseases involving inability to degrade sphingolipids, their accumulation in the nerve tissue leads to neurological manifestations.
- Sphingolipids include sphingomyelin and glycolipids; all contain sphingosine.
- Synthesis of sphingolipids begins with synthesis of ceramide that requires NADPH, FAD, and PLP.
- Sphingolipids can be broken down by different enzymes; each has a specific function.

SUGGESTED TEXTBOOKS

- "Lippincott's Illustrated Reviews in Biochemistry" by P.C.Champe, R.A.Harvey and D.R.Ferrier
- "Harper's Biochemistry" by R.K.Murray, D.K.Granner, P.A. Mayes and V.W.Rodwell.
- Fundamentals of Clinical Chemistry (Tietz) Sixth
- "Textbook of Biochemistry with Clinical Correlations" by T.M.Devlin
- ***www.namrata.co- Biochemistry for medics***

many
Thanks!